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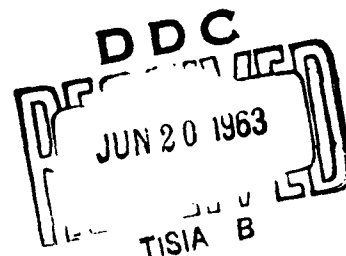
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**EFFECTS OF ANTI- AND PSEUDO-PARKINSON
DRUGS ON SHIVERING**

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**ARCTIC AEROMEDICAL LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
FORT WAINWRIGHT, ALASKA**

Project 8238-22

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ABSTRACT

Effects of atropine, an anti-Parkinson agent, and reserpine, a pseudo-Parkinson agent, on the intensity of shivering in cats were determined. This intensity was measured by the ratio of shivering oxygen consumption rate ($\dot{V}O_2$) to resting $\dot{V}O_2$. At a dose level (5 mg/kg I. P.) in excess of that necessary to suppress Parkinson or experimentally-induced alternating tremor, atropine sulphate had no effect on the intensity of cold-induced shivering. At a dose level of 0.5 mg/kg I. V., reserpine suppressed shivering but evoked an alternating tremor with Parkinson characteristics.

PUBLICATION REVIEW

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EFFECTS OF ANTI- AND PSEUDO-PARKINSON DRUGS ON SHIVERING *

SECTION 1. INTRODUCTION

There are certain similarities and differences in shivering, a cold-induced tremor, and the abnormal tremor of Parkinsonism. This study was designed to show the use of drugs in separating the neurogeneses of these two phenomena. It demonstrates that a drug known to suppress Parkinson tremor has no effect on shivering, while another drug, which suppresses shivering, evokes a tremor some of whose characteristics resemble Parkinson tremor.

Similarities between shivering and Parkinson tremor include the following:

- (1) Both involve alpha motoneuron activation of the skeletal musculature;
- (2) the pyramidal tracts are not involved in either case (Birzis and Hemingway, 1956; Carpenter, 1958), although there is some controversy on this point (Bucy, 1942; Keller, 1948);
- (3) the reticulo-spinal tracts appear to be involved in the mediation of both (Birzis and Hemingway, 1956; Carpenter, 1958);
- (4) both are evoked and maintained by cerebral activity, shivering being of hypothalamic origin (Stuart, 1961) and Parkinson tremor resulting from the pathological sensitization of an as yet ill-defined striatal structure (Carpenter, 1958);
- (5) the rhythm of each appears to be controlled at the spinal level by proprioceptive reflexes (Stuart et al, 1961; Wachs and Boshes, 1961).

The differences between them include the following: (1) Parkinson tremor involves alternating activity of antagonistic muscles (Wycis et al, 1957) whereas shivering may involve synchronous activity of flexors and extensors (Kawamura, 1961); (2) the limb tremor frequency is slower in Parkinson tremor, 4-7 cycles/sec. (Wachs and Boshes, 1961) than during shivering, 10-12 cycles/sec. (Stuart et al, 1961); (3) Parkinson tremor has little metabolic effect (Cooper, 1960) whereas shivering elevates the oxygen consumption rate two- to fourfold above the resting nonshivering level (Stuart, 1961).

Atropine is a drug which suppresses Parkinson tremor (Sollman, 1957) while reserpine induces an alternating tremor with Parkinson characteristics (Barsa and Kline, 1955-6; Weber, 1954). Pseudo-Parkinson tremor can also be produced by electrical stimulation of the midbrain tegmentum (Jenkner and

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Ward, 1953; Wycis et al, 1957) and by electrolytic lesions within the same region (Peterson et al, 1949; Vernier and Unna, 1956). To explain this seeming paradox Ward (1958) has hypothesized that the tremor is driven by "tremorogenic cells" in the midbrain that can be activated by electrical stimulation or become hyperactive after interruption of rostral fibers impinging upon them. He has further postulated that such hyperactivity is a result of the de-afferented "tremorogenic" cells becoming hypersensitive to acetylcholine, released from neighboring reticular cells not affected by the lesion. This could explain how an anti-cholinergic agent such as atropine suppresses Parkinson tremor. If this postulate is correct and if Parkinson tremor and shivering are both mediated via reticulospinal pathways, does this mean that atropine could suppress shivering? Similarly, would a pseudo-Parkinson agent such as reserpine increase the intensity of shivering? Conversely, would not drugs with pseudo- and anti-Parkinson characteristics exert opposite effects on the two forms of tremor since both are in competition for the lower motoneuron pool?

To answer these questions we have tested the effects of these two drugs on the intensity of shivering in cats, as measured metabolically. This involved measurements of shivering and nonshivering oxygen consumption rates before and after the administration of each drug.

SECTION 2. SUMMARY

Effects of atropine, an anti-Parkinson agent, and reserpine, a pseudo-Parkinson agent, on the intensity of shivering in cats were determined. This intensity was measured by the ratio of shivering oxygen consumption rate ($\dot{V}O_2$) to resting $\dot{V}O_2$. In six cats the mean ratio was 3.0 before administration of 5 mg/kg I. P. atropine sulphate. After administration the ratio was 2.6, an insignificant difference. Thus atropine, at a dose level in excess of that necessary to suppress Parkinson or experimentally-induced alternating tremor, had no effect on the intensity of shivering. Since the reticulo-spinal tracts appear to be involved in both shivering and Parkinson tremor, it is suggested that the suppression of the latter by atropine is not by inhibition of multi-synaptic extra-pyramidal pathways in the midbrain or more caudal regions.

In 10 cats the mean ratio of shivering to resting $\dot{V}O_2$ was 3.2 before the administration of 0.5 mg/kg I. V. reserpine. After administration shivering was suppressed, the mean ratio being 1.7, a significant difference ($P < 0.001$). In all cats reserpine evoked an alternating tremor with Parkinson characteristics together with excessive parasympathomimetic activity. It is suggested

that reserpine suppressed shivering by activation of an anterior hypothalamic region known to suppress shivering when stimulated thermally or electrically.

SECTION 3. METHODS

The resting oxygen consumption rates ($\dot{V}O_2$) of six cats were determined at an environmental temperature of 25° to 28° C. They were then exposed to an environmental temperature of 0 to 5° C. Fifteen minutes later, when shivering vigorously, their oxygen consumption rates were again determined. The animals were then given atropine sulphate (5 mg/kg I. P.) and one hour later the resting and shivering oxygen consumption rates determined. The procedure was repeated in three of the six cats several days or weeks later. In 10 other cats the procedure was repeated but the drug was changed to reserpine (0.45-1.5 mg/kg I. V.). Resting and shivering oxygen consumption rates were determined four to five hours after reserpinization.

To determine resting $\dot{V}O_2$ each animal was placed in a 119-liter closed circuit system made of a garbage can with a sealed cover, a water manometer to measure pressure fluctuations and a pump to circulate air. The temperature of the air in the system could be set between 25° and 35° C by regulating the voltage of two 150-watt lamps within the system. $\dot{V}O_2$ was calculated by measuring alterations in pressure and percent CO₂ and O₂ of the closed circuit air. These percentages were continuously recorded by passing a small sample of the air through an infrared CO₂ analyzer (Liston-Becker Company, Model 16) connected to a graphic DC ammeter recorder (Esterline Angus Company, Model AW) and a para-magnetic O₂ analyzer (Arnold O. Beckman, Inc. Model F 3) connected to a graphic AC ammeter recorder (The Bristol Company, Dynamaster Model 1560). Three successive resting 20-minute determinations of $\dot{V}O_2$ were made. During these determinations rectal and air temperatures were continuously recorded.

After the resting (nonshivering) determination the animals were exposed to a second closed-circuit system containing room air at 0 to 5° C. This second system consisted of a sealed copper box placed within a modified household refrigerator (Figure 1). A double glass window, fitted into the top of the refrigerator, permitted observation of the cat. The copper box had a sealed plexiglass window at the top. The gas within the box was circulated by a fan blower, first through a soda-lime CO₂ absorber container and then through a heat exchanger unit. This unit consisted of a copper spiral tube immersed in ice below the box. The previously described analyzers were used to record gas concentrations. A small water manometer recorded

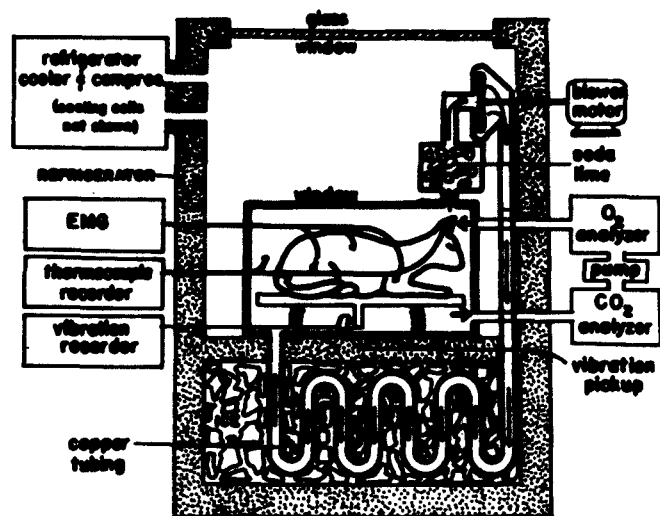


FIGURE 1

Apparatus for measuring intensity of shivering

pressure fluctuations within the system. During shivering $\dot{V}O_2$ determinations, rectal and air temperatures were continuously recorded. The volume of this cold air circuit was determined by a gas dilution method to be 34 liters.

SECTION 4. RESULTS

Atropine Sulphate Administration

Table I summarizes the results on the effects of atropine sulphate on shivering. Before drug administration the animals shivered vigorously with a mean threefold elevation in $\dot{V}O_2$ over the resting nonshivering level. After drug administration they shivered just as vigorously with a mean 2.6 fold elevation in oxygen consumption rate. This difference was of no statistical significance. The animals did not move about while shivering in the cold box but rather adopted a huddled posture with concomitant piloerection. The lack of movement was verified by electromyographic and vibration records, shown schematically in Figure 1.

Although the animals were shivering after drug administration, the rectal temperature of each animal fell significantly during determination of the shivering $\dot{V}O_2$. This indicated excessive heat loss. Piloerection, huddling and cutaneous vasoconstriction are the cat's major heat retentive mechanisms. The assumption of a huddled posture restricts the heat radiating area and piloerection thickens the air insulation layer next to the skin. Since both these mechanisms were evident after atropine administration, it is possible that cutaneous vasoconstriction was impaired.

Atropine sulphate was administered in these experiments in doses of 1, 3 and 5 mg/kg. In all cases shivering was of normal intensity after drug administration. Changes in rectal temperature were recorded after doses of 5 but not after 1 and 3 mg/kg. Therefore, it is not known if cutaneous vasoconstriction was impaired after these two latter doses.

Reserpine Administration

Table II summarizes the results on the effects of reserpine on shivering. Before drug administration the animals shivered vigorously with a mean 3.2 fold elevation in oxygen consumption rate. After administration it was abolished in 3 cats and partially blocked in the other 7. The mean elevation in oxygen consumption rate was 1.7 fold above the resting level. This

TABLE I
EFFECTS OF ATROPINE SULPHATE ON RESTING
AND SHIVERING OXYGEN CONSUMPTION RATE *

Index	R or S	Before Atropine		After Atropine (5.0 mg/Kg I. P.)		Difference	
		\bar{X}	S. D.	\bar{X}	S. D.	Significant	Probability
$\dot{V}O_2$	R	7.5	1.6	8.2	1.2	No	
$\dot{V}O_2$	S	20.3	3.9	19.9	3.6	No	
$\dot{V}O_2$	S/R	3.0	0.9	2.6	0.7	No	
R. T.	R	38.0	0.5	37.9	0.3	No	
R T	R	0.7	0.2	-0.6	0.2	Yes	.005
R T	S	-1.5	1.2	-3.7	2.2	Yes	.05

* Data based on six cats.

$\dot{V}O_2$ Oxygen consumption rate in mls O_2 STPD/Kg/Min.

R. T. Rectal temperature in $^{\circ}C$.

RT Change in rectal temperature during 20 min. $\dot{V}O_2$ determination.

R Resting and non-shivering in warm environment.

S Shivering in cold environment.

\bar{X} Mean value,

S. D. Standard deviation of the mean.

TABLE II

EFFECTS OF RESERPINE ON RESTING AND SHIVERING OXYGEN CONSUMPTION RATE *

Index	R or S	Before Reserpine After Reserpine (0.5 mg/Kg I. V.)				Difference	
		\bar{X}	S. D.	\bar{X}	S. D.	Significant	Probability
$\dot{V}O_2$	R	7.2	1.1	9.1	1.6	Yes	.01
$\dot{V}O_2$	S	22.7	4.5	15.3	3.8	Yes	.001
$\dot{V}O_2$	S/R	3.2	1.0	1.7	1.0	Yes	.001
R. T.	R	38.2	0.3	38.6	0.8	No	
RT	S	-0.8	0.5	-1.8	1.1	Yes	.05

* Data based on 10 cats

$\dot{V}O_2$ Oxygen consumption rate in mls O_2 STPD/Kg/Min.

R. T. Rectal temperature in °C.

RT Change in rectal temperature during 20 min. $\dot{V}O_2$ determination.

R Resting and non-shivering in warm environment.

S Shivering in cold environment.

\bar{X} Mean value.

S. D. Standard deviation of the mean.

decrease was significant ($P < 0.001$). Although shivering was suppressed, the animals moved about the laboratory in a languid fashion, not resisting the imposition of bizarre postures and positions. They also showed excessive parasympathetic activity, that is in terms of extreme salivation, lacrimation, urination, defecation and pupillary constriction.

When left to themselves, alternating tremor was apparent in the four limbs. This was photographed and resembled Parkinson tremor (i. e. 4-7 cycles/sec. and alternating antagonistic muscle activity). This tremor was not apparent when the animals were removed from the cold box, at which time body temperature was low. However, it reappeared when the animals were rewarmed to normal body temperature. This is in contrast to shivering, which appears on cooling and abates on rewarming.

The resting oxygen consumption rate was significantly higher after reserpization ($P < 0.01$). This may have been due to the persistence of the alternating tremor during the determination of resting $\dot{V}O_2$. The significant reduction in the ratio of shivering/resting $\dot{V}O_2$ was not due to the higher denominator value. Table II also shows that the mean shivering $\dot{V}O_2$, the numerator of the ratio, was also significantly depressed after reserpization ($P < 0.001$). The resting rectal temperature of the cats was not affected by reserpization. It did decrease significantly during the determination of shivering $\dot{V}O_2$ ($P < 0.05$) but not to the extent seen after administration of atropine sulphate. Cold-induced huddling and piloerection were present after reserpization.

In three cats shivering was suppressed by 0.25 mg/kg I. V. doses of reserpine. After this dose, alternating tremor was not pronounced. In three other cats shivering was abolished by 1-1.5 mg/kg doses and alternating tremor was most pronounced.

SECTION 5. DISCUSSION

Parkinson tremor (Sollman, 1957) and experimentally induced alternating tremor (Vernier and Unna, 1956) have been effectively blocked with less than 0.5 mg/kg dose of atropine sulphate. It is therefore significant that 1, 3 and 5 mg/kg doses of this drug did not affect the intensity of shivering. If the drug's suppression of alternating tremor is effected by inhibition of multi-synaptic extrapyramidal relays in the midbrain, this would suggest that there are separate extrapyramidal pathways for the conduction of impulses producing shivering and Parkinson tremor. However, available evidence (Birzis and Hemingway, 1956; Carpenter, 1958) would implicate the

reticulo-spinal pathways in the production of both conditions. Thus, it appears that our results conflict with Ward's (1958) hypothesis of experimentally induced alternating tremor resulting from the hypersensitivity of "tremorogenic" de-afferented cells to acetylcholine. The results further suggest that atropine sulphate exerts its suppressive effect on alternating tremor at a more rostral level than the origin of the reticulo-spinal tracts.

The fall in rectal temperature effected by a 5 mg/kg dose of atropine sulphate at both warm and cold environmental temperatures was not accompanied by a lack of cold-induced huddling and piloerection. This may suggest that cutaneous vasoconstriction was impaired by suppression of the activity of a central structure. However, atropine has a direct vasodilatory effect on small blood vessels (Sollman, 1957) that could account for this increased loss of heat.

Shivering was suppressed, rather than completely abolished, by reserpine. This may explain an apparent conflict with the results of Grant and Ahrne (1956). They reported shivering was still present after the administration of reserpine, (0.5 mg/kg) to rabbits exposed to low environmental temperature. However, they found a moderate decline in the oxygen consumption rate of these rabbits in the cold, rather than the two- to fourfold increase one would expect (Stuart, 1961) if the animals were shivering normally.

After reserpine, excessive parasympathomimetic activity was present in all cats, symptomatic of anterior hypothalamic activation. There is a well-defined region at the dorsolateral boundary of the anterior hypothalamus and the preoptic area that, when stimulated thermally (Hemingway et al, 1940; Magoun et al, 1938) or electrically (Andersson, 1956; Hemingway et al, 1954), evokes heat loss mechanisms including the suppression of shivering. It is possible that reserpine activates this region to suppress shivering.

Whether or not physiological tremor was affected by either drug is a matter of conjecture. This form of tremor has the same frequency as shivering (Stuart et al, 1961) and, like shivering, is evident in homeotherms but not poikilotherms (Rohracher, 1959-60). That shivering is a cold-induced exaggeration of the amplitude of the neurological component of physiological tremor is a concept awaiting experimental investigation (Stuart et al, 1961). These experiments have illustrated the use of drugs to separate shivering and alternating tremor. The same principle could be applied to comparing the neurogeneses of shivering and physiological tremor.

REFERENCES

1. Andersson, B. Central control of heat loss mechanism in the goat. *Acta physiol. scandinav.* 37:261-280, 1956.
2. Barsa, J. A. and N. S. Kline. Use of reserpine in disturbed psychotic patients. *Am. J. Psychiat.* 112:684-691, 1955-56.
3. Birzis, L. and A. Hemingway. Descending brain stem connections controlling shivering in the cat. *J. Neurophysiol.* 19:37-43, 1956.
4. Bucy, P. C. Cortical extirpation in treatment of involuntary movements. *Res. Publ. Ass. Nerv. Ment. Dis.* 21:551-595, 1942.
5. Carpenter, M. B. The neuroanatomical basis of dyskinesia. In *Pathogenesis and Treatment of Parkinsonism*, W. S. Fields (ed.), Springfield, Illinois, Chas. C. Thomas, 1958.
6. Cooper, I. S. Results of 1,000 consecutive basal ganglia operations for Parkinsonism. *Ann. Int. Med.* 52:483-499, 1960.
7. Grant, R. and I. M. Ahrne. Reserpine induces hypothermia and antipyresis. 20th Int. Physiol. Congr., Abstr. p. 366, 1956.
8. Hemingway, A., P. Forgrave and L. Birzis. Shivering suppression by hypothalamic stimulation. *J. Neurophysiol.* 17:375-386, 1954.
9. Hemingway, A., T. Rasmussen, H. Wickoff and A. T. Rasmussen. Effects of heating the hypothalamus of dogs by diathermy. *J. Neurophysiol.* 3:329-338, 1940.
10. Jenkner, F. L. and A. A. Ward Jr. Bulbar reticular formation and tremor. *A.M.A. Arch. Neurol. Psychiat.* 70:489-502, 1953.
11. Kawamura, Y. Neuromuscular organization of shivering. In *Proceedings, Symposia on Arctic Biology and Medicine. I. Neural Aspects of Temperature Regulation*. Arctic Aeromedical Laboratory, 1961.
12. Keller, A. D. Descending nerve fibers subserving heat maintenance functions coursing with cerebrospinal tracts through the pons. *Am. J. Physiol.* 154:82-86, 1948.

13. Magoun, H. W., F. Harrison, J. R. Brobeck and S. Ranson. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* 1:101-114, 1938.
14. Peterson, R. W., H. W. Magoun, W. S. McCullough and D. B. Lindsley. Production of postural tremor. *J. Neurophysiol.* 12:371-384, 1949.
15. Rohrer, H. Standige muskelaktivitat ("Mikrovibration"), tonus und Konstanz der Korpertemperatur. *Z. Biol.* 111:38-53, 1959/60.
16. Sollman, T. *A Manual of Pharmacology*, Philadelphia, W. B. Saunders Co., 1957, p. 389.
17. Stuart, D. G. Role of the prosencephalon in shivering. *In Symposia on Arctic Biology and Medicine. I. Neural Aspects of Temperature Regulation.* Arctic Aeromedical Laboratory, 1961.
18. Stuart, D. G., E. Eldred, A. Hemingway and Y. Kawamura. Neural regulation of the rhythm of shivering. *In Temperature - Its Regulation in Science and Industry*, C. M. Herzfeld (ed.), Washington, Reinhold Publishing Corp., in press, 1961.
19. Vernier, V. E. and K. R. Unna. The experimental evaluation of anti-Parkinson compounds. *Ann. N.Y. Acad. Sci.* 64:690-704, 1956.
20. Wachs, H. and B. Boshes. Tremor studies in normals and Parkinsonism. *A.M.A. Arch. Neurol. Psychiat.* 4:66-82, 1961.
21. Ward, A.A. Jr. Physiological basis of involuntary movement. *In Pathogenesis and Treatment of Parkinsonism*, W. S. Fields (ed.), Springfield, Chas. C. Thomas, 1958.
22. Weber, E. Ein rauwolfiaalkaloid in der psychiatrie: seine wirkungsahnlichkeit mit Chlorpromazin. *Schweiz. med. Wchnschr.* 84:968-970, 1954.
23. Wycis, H. T., E. G. Szekeley and E. A. Spiegel. Tremor on stimulation of the midbrain tegmentum after degeneration of the brachium conjunctivum. *J. Neuropath. Exper. Neurol.* 16:79-84, 1957.

<p>Arctic Aeromedical Laboratory, United States Air Force (AFSC), APO 731, Seattle, Wash. Rpt. AAL-TDR-62-17. EFFECTS OF ANTI- AND PSEUDO-PARKINSON DRUGS ON SHIVERING. September 1962. 11 p. incl. illus., tables.</p> <p>Unclassified Report</p> <p>Effects of atropine, an anti-Parkinson agent, and reserpine, a pseudo-Parkinson agent, on the intensity of shivering in cats were determined. This intensity was measured by the ratio of shivering oxygen consumption rate ($\dot{V}O_2$) to resting $\dot{V}O_2$. At a dose level (5 mg/kg I.P.) in excess of that necessary to suppress Parkinson or experimentally-induced alternating tremor, atropine sulphate had no effect on the intensity of cold-induced shivering. At a dose level of 0.5 mg/kg I.V., reserpine suppressed shivering but evoked an alternating tremor with Parkinson characteristics.</p>	<p>Shivering Atropine Reserpine Cats</p> <p>Project 8238-22 Contract AF41(657)-344 Univ. of California at Los Angeles Stuart, D. G., R. George W. J. Freeman, A. Hemingway, W. M. Price Available from OTS In ASTIA collection</p>	<p>I. II. III. IV. V. VI.</p>	<p>Shivering Atropine Reserpine Cats</p> <p>Project 8238-22 Contract AF41(657)-344 Univ. of California at Los Angeles Stuart, D. G., R. George W. J. Freeman, A. Hemingway, W. M. Price Available from OTS In ASTIA collection</p>	<p>I. II. III. IV. V. VI.</p>	<p>Shivering Atropine Reserpine Cats</p> <p>Project 8238-22 Contract AF41(657)-344 Univ. of California at Los Angeles Stuart, D. G., R. George W. J. Freeman, A. Hemingway, W. M. Price Available from OTS In ASTIA collection</p>	<p>I. II. III. IV. V. VI.</p>
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